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09/484,048	01/18/2000	Stig Steen	33314WC548931	9191

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EXAMINER
AFREMOVA, VERA

ART UNIT	PAPER NUMBER
1651	20

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/484,048	Applicant(s) Steen
	Examiner Vera Afremova	Art Unit 1651

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 15, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above, claim(s) *2-4 and 8-23* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 5-7, and 24-34* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *1,6,12*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Prosecution Application

The request filed on 4/15/2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/484,048 is acceptable and a CPA has been established. An action on the CPA follows.

Claims 1-34 are pending.

Claims 2-4, 8-23 were withdrawn from consideration as being drawn to non-elected inventions. Applicant elected without traverse the invention of original claims 1 and 5-7. [Paper No. 7 filed 1/25/2001].

Claims 1, 5-7, 24-32 and new claims 33 and 34 are under examination in the instant office action. [Paper No. 10 filed 6/08/2001 and Paper No. 19 filed 4/15/2002].

Claim Rejections - 35 USC § 112

New matter

New claims 33 and 34 are rejected under 35 U.S.C. 112, *first paragraph,* as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention..

Insertion of the limitation such as "for more than 36 hours" and/or "for more than 36 hours at 0.5-12°C" in the method for preserving organs of claims 33 and 34 has no support in the

as-filed specification. The insertion of this limitation is a new concept because it neither has literal support in the as-filed specification by way of generic disclosure, nor are there specific examples of the newly limited genus which would show possession of the concept of the use of storing time "for more than 36 hours" and/or "for more than 36 hours at 0.5-12°C". There is only a generic disclosure directed to the use of preservation solution for a period of time which does not exceed 36 hours. For example: see specification page 17, line 20, wherein the time period is limited "up to 36 hours". The other example: see at page 28, wherein the time period is limited "for at most 36 hours" at the temperature within the claimed range 0.5-12°C. The exemplified disclosure (fig. 1) demonstrates contractions of rat aorta which is stored or kept for 48 hours during experiment. But the temperature is not limited by any particular temperature and, thus, the aorta contractions are reasonably expected to be tested at room temperature which is not "0.5-12°C" but rather about 25°C. This is not sufficient support for the new genus such as "for more than 36 hours" and/or "for more than 36 hours at 0.5-12°C". This is a matter of written description, not a question of what one of skill in the art would or would not have known. The material within the four corners of the as-filed specification must lead to the generic concept. If it does not, the material is new matter. Declarations and new references cannot demonstrate the possession of a concept after the fact. Thus, the insertion of the limitations such as "for more than 36 hours" and/or "for more than 36 hours at 0.5-12°C" in the method for preserving organs of claims 33 and 34 is considered to be the insertion of new matter for the above reasons.

Indefinite

Claims 1, 5-7, 24-32 and new claims 33 and 35 are rejected under 35 U.S.C. 112, *second paragraph,* as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rendered indefinite by the phrase "improved" because it fails to point out what substitute the improvement as intended.

Claim 5 is rendered indefinite by the phrases "improved" and "optionally" because it is uncertain under what conditions nitroglycerin is not required and what make the claimed composition "improved". The exclusion of nitroglycerin results in a failure to point the subject matter which applicant regards as the invention in the light of the applicant's showing and arguments directed to synergistic effects of calcium and nitroglycerin in the claimed "improved" compositions. What is the difference in the intended improvements in the compositions of claim 1 and 5?

Claim 6 is rendered in definite by the phrase "THAM" buffer in the lack of definitions or a reference to the claimed buffer/product. What is a difference in contents and function between "THAM" buffer and "phosphate buffer", particularly, when both are present in one composition?

Claim 26 contains some typing error in the word "saphena".

Claim 31 is rendered indefinite by the phrase "exposing" because neither conditions or particular active step or manipulations is/are as uncertain as claimed and as disclosed.

Claim 32 is rendered indefinite by the phrase "maintaining the integrity" in the lack of definitions what is regarded as "maintaining the integrity". What is structure or function, for example?

Claims 33 and 34 are indefinite because storage time is uncertain as claimed and as disclosed. There is a typing error in the claimed temperature range wherein "0" is missing in "0.5".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5, 7, 24-29, 31 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wlakenbach et al. [IDS-12, AO, 1991] taken with Ingemansson *et al.* [IDS-12, AN, 1995] and Ingemansson *et al.* [IDS-1, AT-2, 1995].

Claims are directed to a preservation solution which does not comprise nitroglycerin and which comprises calcium, about 1-15% of colloidosmotically active substance or dextran 40, glucose, buffer and ions of potassium, magnesium and sodium. Some claims are further drawn to a method for preserving organs or tissues by storing the organs or tissues in the claimed solution

for less than 36 hours at 0.5-12°C and/or for more than 36 hours at 0.5-12°C. Some claims are further drawn to methods for preservation of various organs and tissues of animals including tissues with blood vessels, veins, vascular endothelium and/or contractile tissues.

Wlakenbach et al teaches a preservation solution which does not comprise nitroglycerin and which comprises calcium, about 1-15% of dextran 40, buffer, glucose and ions of potassium, magnesium and sodium. The reference also teaches a method for preserving organs or tissues such as cornea, for example, by storing them in the preservation solution at low temperature including 4°C or between 0.5 and 12°C for a period of time such as about 7 days including time periods such as more than 36 hours and less than 36 hours.

The cited reference by Wlakenbach et al discloses the use of two particular preservation solutions comprising components at narrow concentration ranges as designed for corneal tissue applications. But it is lacking disclosure related to preservation of other organs and tissue including vascular endothelium, blood vessels and/or contractile tissues, for example.

But the cited references by Ingemansson *et al.* [IDS-12, AN, 1995] and Ingemansson *et al.* [IDS-1, AT-2, 1995] teach the use of various solutions in the methods for preservation of various organs and tissues of animals including tissues with blood vessels, veins, vascular endothelium and/or contractile tissues wherein solutions comprise calcium, colloidosmotically active substance or dextran, glucose, buffer and ions of potassium, magnesium and sodium at various concentrations. The reference by Ingemansson *et al.* [IDS-1, AT-2, 1995] teaches that Perfadex solution comprising colloidosmotically active substance manifests superior effects

related to preservation of contractile tissues. The reference by Ingemansson *et al.* [IDS-12, AN, 1995] teaches that incorporation of calcium ion into storage or organ-bath solutions resulted in preservation of a contractile capacity of animal tissues for a period of time more than 36 hours and it suggests incorporation of calcium into various preservation solutions including Perfadex, for example (page 1181, col. 1, par. 3).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to obtain solutions comprising calcium, colloidosmotically active substance, glucose, buffer and ions of potassium, magnesium and sodium with a reasonable expectation of success in preserving biological activity of animal organs and tissues because the prior art teaches and suggests the use of solutions with the same components as the claimed solution at concentrations substantially similar to the claimed solution in the methods for preservation of various organs ans tissues. One of skill in the art would have been motivated to include calcium into preservation or storage solutions intended for various grafts including tissues with blood vessels, veins, vascular endothelium and/or contractile tissues because the prior art suggests incorporation of calcium for preservation of biological activity of grafts including contractile capacity. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Claims 1, 5-7, 24-32 and new claims 33 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wlakenbach et al. [IDS-12-AO, 1991] taken with Ingemansson *et al.* [IDS-12-AN, 1995] and Ingemansson *et al.* [IDS-1, AT-2, 1995] as applied to claims 5, 7, 24-29, 31 and 34 above, and further in view of Pinsky *et al.* [IDS-1, AQ-2, 1994] and Naka *et al.* [IDS-1, AT-1, 1995].

Claims 5, 7, 24-29, 31 and 34 as explained above. Claims 1, 6, 30, 31, and 34 are/~~are~~ further drawn to incorporation of nitroglycerin into preservation solutions for storing and/or preserving organ and tissues.

The cited references by Wlakenbach et al. [IDS-12, AO, 1991], Ingemansson *et al.* [IDS-12, AN, 1995] and Ingemansson *et al.* [IDS-1, AT-2, 1995] are relied upon as explained above. They are lacking teaching drawn to the inclusion of nitroglycerin into solutions in the method for preservation of animal organs and tissues.

However, the references by Pinsky et al and by Naka et al teach that incorporation of nitroglycerin in storage or preservation solution enhances survival of animal tissue or organ grafts (see abstracts), that nitroglycerin maintains vascular homeostasis in animal organs and tissues and that nitroglycerin is added to solutions intended for both perfusion and preservation including Ringer's solution which contains calcium. The suggested amounts of nitroglycerin are about 0.1 mg/ml.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to include nitroglycerine in storage or preservation solutions as

taught by Pinsky *et al.* and Naka *et al* with a reasonable expectation of success and with the expected benefit if maximizing the preservation of animal organs and tissue useful, for example, for transplantation because the prior art teaches that incorporation of nitroglycerin into storage solutions including preservation solutions with calcium enhances survival of animal tissue or organ grafts and that nitroglycerin maintains vascular homeostasis in animal organs or integrity of animal tissues. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Response to Arguments

Applicant's arguments filed 4/15/2002 [Paper No. 19] have been fully considered but they are not persuasive.

Applicant's main argument is directed to the synergistic effects of calcium and nitroglycerin (see response page 5). However, the solution of claims 5 and 7 and the method of claims 24-29, 31 and 34 does not require incorporation of nitroglycerin by the virtue of the phrase "optionally".

Further, the evidence necessary to overcome a *prima facie* case of obviousness must not only be clear and convincing, but must also be commensurate in scope with the claimed subject matter.

For example: the solutions of claims 1, 6 and 33 require a combination of both calcium and nitroglycerin but the claimed solutions are not limited to particular amounts of calcium and nitroglycerin which produce synergistic effects as argued. Moreover, the solutions of claim 1 and 33 are not limited to the any ingredients which are commonly used in the preservation solutions and which are reasonably expected for animal tissue and organ preservation.

Further, the particular solutions in the method of claims 30 and 32 are limited to the presence of particular amounts of nitroglycerin and calcium but these solutions also require incorporation of colloidosmotically active substances of at least two molecular weights (claim 5). The particular applicant's showing (Fig. 1), which is argued as a support for synergistic effect of calcium-nitroglycerin combination, demonstrates animal tissue contractile capacity and encompasses the use of the solution Perfadex which contains dextran 40 or the use of a colloidosmotically active substances of only one molecular weight. Moreover, the amounts of calcium and nitroglycerin used in Fig. 1 do not delineate clearly the amounts of calcium and nitroglycerin required to obtain the touted synergistic result. Further more, neither specification nor arguments are particularly clear with regard to the claimed effects such as "maintaining the integrity" (see claim 32, for example), in particular, as related to the synergistic combination of calcium and nitroglycerin as argued.

Thus, the applicant's showing and arguments do not commensurate in scope with the claimed subject matter. The allegation that limited data is sufficient to establish the existence of synergism from other such ingredients is without merit. It is well recognized that synergism is a

highly unpredictable result which is very dependent on the ingredients used and the amounts of each. Thus any combination for which synergism is not clearly established would be properly rejected because non-obviousness would not have been established.

Some of the applicants arguments are directed to the differences between irrigation and preservation solutions and to the intended use of the claimed solutions for preservation of blood vessels, for example: response page 3-4 . However, the intended use of a solution does not distinguish this solution since such undisclosed use is inherent in the prior art solution comprising same or similar components. It is also noted that the references cited in the office action teach preservation solutions rather than irrigation solutions as argued. Further, in order to be limiting, the intended use must create a structural difference between the claimed solution the prior art solution. In the instant case, the intended use does not create a structural difference, thus, the intended use is not limiting. Moreover, the cited prior art references {Ingemansson *et al.* [IDS-12, AN, 1995] and Ingemansson *et al.* [IDS-1, AT-2, 1995]} teach the preservation solutions for animal organ and tissues including vascular endothelium, blood vessels and/or contractile tissues which as encompassed by the claimed invention. "The claiming of a new use . . . which is inherently present in the prior art does not necessarily make the claim patentable." *In re Best*, 195 USPQ 430, 433 (CCPA 1977). When applicant claims a "composition in terms of function . . . and the composition of the prior art is substantially similar as that of the claim but the function is not explicitly disclosed by the reference, the rejection is proper. (MPEP 2112).

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (703) 308-9351. The examiner can normally be reached on Monday to Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vera Afremova

Art Unit 1651

June 20, 2002.

Irene Marx

IRENE MARX
PRIMARY EXAMINER